

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE  
BEFORE THE BOARD OF PATENT APPEALS AND  
INTERFERENCES**

In re Application of:

UMEK et al.

Application No. 09/626,096

Filed: July 26, 2000

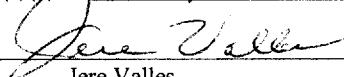
For: Sequence Determination of Nucleic  
Acids Using Electronic Detection

Examiner: CALAMITA, Heather

Art Unit: 1637 Conf. No.: 8157

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**AMENDED APPEAL BRIEF**

This Amended Appeal Brief is filed in support of Appellant's appeal from the Final Rejection of February 7, 2008. A Notice of Appeal was filed on July 7, 2008. A first Appeal Brief was filed on January 7, 2009, with a petition for four-month extension.

This Amended Appeal Brief is filed to correct the identity of the Real Party in Interest, which is Osmetech Technology Inc., the assignee of the present application. No other changes have been made to this Brief.

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**REAL PARTY IN INTEREST**

The real party in interest in this appeal is Osmetech Technology Inc., the assignee of the present application.

**RELATED APPEALS AND INTERFERENCES**

No other appeals or interferences are known to Appellants, the undersigned Appellants' representative or the assignee to whom the inventors assigned their rights in the instant case, that would directly affect, be directly affected by or bear on the Board's decision in the instant appeal.

### **STATUS OF THE CLAIMS**

Claim 1-59 are canceled. Claims 60-69 as presented in the Amendment filed April 7, 2008, are rejected and under appeal.

### **STATUS OF THE AMENDMENTS**

No amendment to claims has been made or entered after the Final Rejection of February 7, 2008 (“the Final Rejection”).

## SUMMARY OF THE CLAIMED SUBJECT MATTER

Claim 60 is the only pending independent claim in this application. Claims 61-69 depend from claim 60.

Claim 60 is directed to a method of determining the identification of nucleotide(s) at a first detection position in a first domain of a target sequence comprising said first domain and a second domain. The method comprises the steps of (a) providing an electrode with a covalently attached capture probe, wherein said capture probe has a sequence substantially complementary to said second domain of said target sequence; (b) contacting said electrode with: (i) said target sequence; (ii) a first label probe substantially complementary to said first domain, comprising a first nucleotide at an interrogation position and a first electron transfer moiety (ETM) with a first redox potential; and (iii) a second label probe substantially complementary to said first domain, comprising a second nucleotide at said interrogation position and a second ETM with a second redox potential, under conditions wherein if said nucleotide at said interrogation position is perfectly complementary to said detection position, hybridization of said probe(s) occurs; and (c) detecting the presence of said first and/or second ETM to determine the nucleotide(s) at said detection position. This aspect of the invention is described, *inter alia*, on page 3, lines 31-36; page 15, line 31 to page 16, line 5; page 16, lines 13-37; page 30, lines 16-27 and 37-39; in Figure 3C; and in Example 4.

**GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL**

Claims 60-69 are allegedly unpatentable under 35 USC 103(a) over Kayyem et al., PCT Publication WO/1998/020162 (published May 14, 1998), in view of Shuber, US Patent 5,633,134 (issued May 27, 1997).

## ARGUMENT

***Rejection under 35 USC 103(a) over Kayyem et al., PCT Publication WO/1998/020162, in view of Shuber, US Patent 5,633,134***

### Claims 60 to 69

Claims 60-69 are finally rejected under 35 USC 103(a) over Kayyem et al., PCT Publication WO/1998/020162, in view of Shuber, US Patent 5,633,134.

Claim 60 recites

A method of determining the identification of nucleotide(s) at a first detection position in a first domain of a target sequence, said target sequence comprising said first domain and a second domain, said method comprising:

- a. providing an electrode with a covalently attached capture probe, wherein said capture probe has a sequence substantially complementary to said second domain of said target sequence;
- b. contacting said electrode with:
  - (i) said target sequence;
  - (ii) a first label probe substantially complementary to said first domain, comprising a first nucleotide at an interrogation position and a first electron transfer moiety (ETM) with a first redox potential;
  - (iii) a second label probe substantially complementary to said first domain, comprising a second nucleotide at said interrogation position and a second ETM with a second redox potential;
- c. detecting the presence of said first and/or second ETM to determine the nucleotide(s) at said detection position.

In the Final Rejection, the Examiner alleges that Kayyem teaches all of the limitations of claim 60, except that “Kayyem et al. do not teach step (iii) a second label probe complementary to the first domain comprising a second nucleotide at said interrogation position.” To cure this deficiency, the Examiner cites Shuber, which allegedly teaches “multiple oligonucleotide probes with labels for determining

nucleotides at the detection position (see abstract and col. 5 lines 13-21 and table 1, where the ASOs [allele specific oligonucleotides] are the labeled probes used to detect the mutations at the interrogation position)[.]” As a motivation to combine, the Examiner states that

it would have been *prima facie* obvious to one of ordinary skill in the art to use the ETM labeled oligonucleotides, as taught by Kayyem et al. with the multiple oligonucleotide probes for mutation detection, as taught by Shuber since Kayyem states, ‘In general electron transfer between electron donors and acceptors does not occur at an appreciable rate when the nucleic acid is single stranded, nor does it occur appreciably unless nucleotide base pairing exists in the double stranded sequence between the electron donor and acceptor in the double helical structure (see p. 9 lines 21-24).’

The Examiner thus alleges that all of the elements of the claims are taught by the combination of Kayyem and Shuber and provides an alleged reason to combine the elements such that the invention as claimed in claim 60 and claims dependent therefrom is obvious. As set forth below, the Examiner has failed to properly perform the factual inquiry required by the Supreme Court in *KSR Int'l. Co. v. Teleflex Inc.*, 127 S.Ct. 1727 (2007). Further, the Examiner has failed to set forth “a reason to combine the known elements in the fashion claimed” by the claims at issue. *Id.* at 1741. Thus, it will be shown that the Examiner has failed to establish a *prima facie* case of obviousness under the law of *KSR*.

*The Examiner has failed to properly analyze the Graham factors that form the basis for an obviousness rejection.*

35 USC 103(a) states that

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

In *KSR Int'l. Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1734 (2007), the Supreme Court reaffirmed the analysis that it had previously set forth in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966), reiterating that “[u]nder § 103, the scope and content of the prior art to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined.” The

Court stated that “while the sequence of these questions might be reordered in any particular case, the factors continue to define the inquiry that controls.” *Id.* Thus, obviousness is a question of law based on underlying facts. *Fromson v. Anitec Printing Plates, Inc.*, 132 F.3d 1437, 1447 (Fed. Cir. 1997). The determination of whether the subject matter as a whole would have been obvious to a person of ordinary skill at the time the invention was made is reviewed by a court for correctness as a matter of law, and the underlying factual determinations are reviewed for clear error. *Id.*

*Level of ordinary skill in the art*

The Examiner has not provided in the record any indication of the level of ordinary skill in the art. The Examiner’s factual inquiry into the *Graham* factors is therefore incomplete at least in this respect. Appellants note that the Federal Circuit has found a person of ordinary skill in the art generally “to be one who thinks along the line of conventional wisdom in the art and is not one who undertakes to innovate, whether by patient, and often expensive, systematic research or by extraordinary insights.” *Standard Oil Co. v. American Cyanamid Co.*, 774 F.2d 448 (Fed. Cir. 1985).

*Scope and content of the prior art*

Kayyem discloses nucleic acids covalently coupled to electrodes via conductive oligomers. Kayyem, p. 1., line 1. Various aspects of the invention disclosed by Kayyem include

compositions comprising electrodes with conductive oligomers attached to probe nucleic acids, without second electron transfer moieties, and soluble second probe sequences with second electron transfer moieties. Upon binding of the target sequence, which contains a first target domain for the first probe sequence and a second target domain for the second probe sequence, which preferably are adjacent, electron transfer may occur.

Kayyem, p. 36, lines 10-14.

Shuber is directed to testing “for the presence or absence of multiple mutations in one gene or multiple genes using ASO probes in the presence of a quaternary ammonium salt which eliminates disparities in the melting temperatures of the ASO used.” See Shuber, abstract. According to Shuber, column 1, lines 58-60, “a DNA sample is hybridized with multiple mutation specific ASO probes of approximately the same length.” The multiple ASO probes *all have the same label*. Thus, in a first Example, Shuber, column 5, lines 20, 21, 39 and 40, states that “<sup>32</sup>P-labeled mutation specific ASO probes[] were made from the ASO sequences shown [i]n Table 1. Hybridizations were carried out in plastic bags containing pooled <sup>32</sup>[P]-labelled ASO probes shown in Table 1[.]” Results are provided in “autoradiographs prepared by exposure to Kodak X-OMAT

AR X-ray film.” Id., col. 5, lines 55-56. Shuber tests for 12 mutations by dividing the ASO probes in Table 1 into 4 groups and performing 4 individual hybridizations. See Shuber, col. 6, lines 66 & 67. Shuber then discloses that “pool-positive samples were subsequently hybridized independently with the relevant ASOs to identify the specific mutation or mutations involved.” See Shuber, col. 7, lines 27-29. Thus, having identified which pool of probes provides positive results, each probe of the pool is hybridized individually to determine whether the sample contains mutations according to the probe. Throughout the entire process, the *same* label, <sup>32</sup>P, is used on all of the probes. Thus, using the methods of Shuber, the detectable signal from any given probe is *indistinguishable* from the signal of any other probe. In the second and final example of Shuber, “the same protocol was followed as in Example 1” except additional probes were added to one of the four pools. However, there is no indication that any label other than <sup>32</sup>P was incorporated into these probes. The specification of Shuber apart from the Examples teaches the use of only one type of label with the probes for any given experimental determination of “multiple mutations.” Thus, Shuber teaches determining mutations through a process of elimination that uses only the same, indistinguishable probe in any hybridization experiment.

*Differences between the prior art and the claims at issue*

Claim 60 recites using at least two different label probes, in which a first label probe comprises a first electron transfer moiety (ETM) with a first redox potential and a second label probe comprises a second ETM with a second redox potential. According to the claims, if a nucleotide at an interrogation position of a probe is perfectly complementary to a detection position of a target sequence, hybridization of the probe occurs and a signal unique to the probe would be detected. Thus, whether the first label probe or the second label probe hybridizes can be determined based on the distinct signals characteristic of the respective ETMs. The claims thus have the advantage, for example, of allowing the practitioner to *distinguish the binding of two different label probes of different sequence in the same experimental run*. Thus, for example, the experiment can determine whether the sample is a homozygote or a heterozygote in a single assay. For example, given a particular SNP (e.g. the wild type allele is a “T” and the SNP variant is a “C” at a particular position), the present invention can determine whether a sample is homozygotic wild-type (e.g. only the label associated with the “T” is present), homozygotic variant (e.g. only the label associated with the “C” is present), or heterozygotic (both labels appear). See, e.g., Example 3 of the specification. This will not work if the labels associated with the “T” and “C” probes are the same, such as taught by

Shuber; in Shuber the signal from the two probes would be indistinguishable and would render the invention inoperative.

As admitted by the Examiner on page 3 of the Final Rejection, “Kayyem et al. do not teach step (iii) a second label probe complementary to the first domain comprising a second nucleotide at said interrogation position.” To cure this deficiency, the Examiner asserts in the Final Rejection, particularly on page 4, and in the Advisory Action that Shuber teaches a second ETM with a second redox potential because “Shuber teaches multiple oligonucleotide probes with labels.”

Shuber, however, does not disclose a second label probe comprising a second ETM with a second redox potential. As discussed above, the multiple ASO probes in Shuber *all have the same label*. Nowhere does Shuber disclose using more than one probe in which at least one probe is labeled in such a manner that can be distinguished in the same experimental run. While Shuber does disclose that “ASOs can also be labelled by non-isotopic methods (e.g. via direct or indirect attachment of fluorochromes or enzymes, or by various chemical modifications of the nucleic acid fragments that render them detectable immunochemically or by other affinity reactions)[,]” (col. 3 , lines 9-12), this description does not disclose to one of skill in the art to use labels having distinguishable signals in an experiment; at best, it suggests using labels other than  $^{32}\text{P}$ . In the context of Shuber as a whole, which teaches determining mutations by the process of elimination, one of skill in the art *would not have interpreted Shuber as teaching the use of multiple different labels simultaneously*. Merely providing examples in which multiple oligonucleotide probes can be used does not disclose to one of skill in the art the more specific use of at least two different label probes, each having an ETM with a unique, distinguishable redox potential.

In further support of the contention that Shuber teaches a second ETM with a second redox potential, the Examiner states on page 5, paragraph 1 of the Final Rejection that “Shuber teaches a first step using multiple probes and if a positive result is present then in a second step a second probe is used to determine which mutation is present.” However, as discussed above, this “second probe” is not in fact a different probe with distinguishable characteristics compared to those used in the first step of Shuber, but merely one or more of the *same* probes of the first step used a second time. Thus, the methods and examples taught by Shuber do not teach the use of *at least two different label probes, each having an ETM with a unique, distinguishable redox potential*. Shuber only fairly discloses using, in the same experiment, more than one probe in terms of number and not in terms of a distinguishable type of signal.

In alleging that Kayyem teaches the limitation of a second ETM label with a second redox potential, the Examiner on page 5, paragraph 2 in the Final Rejection and the Advisory Action of May 1, 2008, cites Kayyem at page 52, lines 6-24, and states that “Kayyem teaches a first ETM label on a first oligonucleotide and a second ETM label on a second oligonucleotide.” This inference is based on a clear error of fact. Kayyem, on page 52, lines 6 and 7, teaches “compositions comprising a) a first single stranded nucleic acid covalently attached to an **electrode** via a conductive oligomer and b) a second single stranded nucleic acid containing a second electron transfer moiety[.]” Thus, in this embodiment of Kayyem, there are two ETMs, the first ETM being an electrode, which does not function as a label and the second of which is a true label. In contrast, claim 60 recites three ETMs: an electrode, a first ETM with a first redox potential and a second ETM with a second redox potential. In claim 60, the electrode is contacted with at least two label probes, each having an ETM with a distinct redox potential, whereas in the Kayyem embodiment, the electrode is contacted with one type of label probe having an ETM with one redox potential. Kayyem therefore does not teach all of the limitations of the claims.

Kayyem and Shuber in combination thus do not disclose contacting an electrode with at least a second label probe comprising a second ETM with a second redox potential, and thus do not teach each and every limitation of the claims as implied by the Examiner. An erroneous factual determination according to the *Graham* factors thus forms the basis for the Examiner’s inquiry into whether the claimed invention is obvious.

*The Examiner has failed to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.*

Having made a fact determination under *Graham*, the Examiner must provide “some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” *KSR* at 1741 (citing *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)). Merely demonstrating that each of the elements of a claim is independently known in the prior art is not sufficient to prove that the claim is obvious. *Id.* Rather, “it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.” *Id.* Thus, it will be often necessary to look to interrelated teachings of multiple patents, for example, “in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed[.]” *Id.* at 1740-41; see also *In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004) (“When a rejection depends on a combination of prior art

references, there must be some teaching, suggestion, or motivation to combine the references.”).

The Examiner states that

it would have been *prima facie* obvious to one of ordinary skill in the art to use the ETM labeled oligonucleotides, as taught by Kayyem et al. with the multiple oligonucleotide probes for mutation detection, as taught by Shuber since Kayyem states, ‘In general electron transfer between electron donors and acceptors does not occur at an appreciable rate when the nucleic acid is single stranded, nor does it occur appreciably unless nucleotide base pairing exists in the double stranded sequence between the electron donor and acceptor in the double helical structure (see p. 9 lines 21-24). An ordinary practitioner would have been motivated to use ETM labeled oligonucleotides, as taught by Kayyem et al. with the multiple oligonucleotide probes for mutation detection because Kayyem states that no electron transfer occurs unless nucleotide base pairing exists in the double stranded sequence between the electron donor and acceptor.

As argued above, the Examiner has failed to properly perform the *Graham* factual inquiry required by the Court in *KSR*. Neither Kayyem nor Shuber, alone or in combination, explicitly disclose using a second label probe comprising a second ETM with a second redox potential. Thus, the Examiner, relying on Kayyem and Shuber, without more, could not have reached the question of “reason to combine the elements in the way the claimed new invention does” since the “elements” of the claimed invention have not been properly identified. Claim 60 does not generally recite “multiple probes” but rather, a second label probe comprising “a second ETM with a second redox potential.” As discussed above, Shuber only discloses that the probes used to detect mutations should be “multiple” in number, *not that the probes should carry labels having multiple, distinct signaling characteristics*. Shuber in combination with Kayyem does not teach this and the Examiner has not provided any further rationale for how one of skill in the art would make this leap. Thus, the claimed invention does not follow from the combination of Shuber and Kayyem, even were there motivation to combine them. In this way, the Examiner has not shown, as required by *KSR*, that “a person of ordinary skill in the relevant field [would] combine the elements in the way the claimed new invention does[.]” The obviousness of the claims in view of the references therefore has not been established.

### ***Relief Requested***

Appellants have shown that the rejections under 35 USC 103(a) over Kayyem and Shuber cannot be maintained because the Examiner has failed to make a proper factual

determination according to the *Graham* factors and has not provided a proper reason why the claimed invention as a whole is obvious in view of the references. The Examiner has thus failed to establish a *prima facie* case of obviousness.

Appellants therefore respectfully request that the rejection of Claims 60-69 over Kayyem and Shuber be withdrawn and that Claims 60-69 be allowed.

Authorization is granted to charge any outstanding fees due at this time for the continued prosecution of this matter to Morgan, Lewis & Bockius LLP Deposit Account No. 50-0310 (Client-Matter No. 067456-5030-US). In the unlikely event that the fee transmittal or other papers are separated from this document and/or other fees or relief are required, Appellants petition for such relief, including extensions of time, and authorize the Commissioner to charge any fees under 37 CFR 1.16, 1.17 and 1.21 which may be required by this paper, or to credit any overpayment, to deposit account number 50-0310, order no. 067456-5030-US.

Respectfully submitted,

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## CLAIMS APPENDIX

60. A method of determining the identification of nucleotide(s) at a first detection position in a first domain of a target sequence, said target sequence comprising said first domain and a second domain, said method comprising:

- a. providing an electrode with a covalently attached capture probe, wherein said capture probe has a sequence substantially complementary to said second domain of said target sequence;
- b. contacting said electrode with:
  - (i) said target sequence;
  - (ii) a first label probe substantially complementary to said first domain, comprising a first nucleotide at an interrogation position and a first electron transfer moiety (ETM) with a first redox potential;
  - (iii) a second label probe substantially complementary to said first domain, comprising a second nucleotide at said interrogation position and a second ETM with a second redox potential;
- c. detecting the presence of said first and/or second ETM to determine the nucleotide(s) at said detection position.

61. The method of Claim 60 wherein said method further comprises contacting said electrode with a third label probe substantially complementary to said first domain, comprising a third nucleotide at said interrogation position and a third ETM with a third redox potential.

62. The method of Claim 61 wherein said method further comprises contacting said electrode with a fourth label probe substantially complementary to said first domain, comprising a fourth nucleotide at said interrogation position and a fourth ETM with a fourth redox potential.

63. The method of Claim 60 wherein said electrode comprises an array of capture probes, each substantially complementary to a second domain of a different target sequence.

64. The method of Claim 60 wherein said first label probe contains a plurality of first ETMs.

65. The method of Claim 60 wherein said second label probe contains a plurality of second ETMs.

66. The method of Claim 60 wherein said electron transfer moieties comprise a transition metal complex.

67. The method of Claim 66 wherein said transition metal complex comprises a metallocene.

68. The method of Claim 67 wherein said metallocene is a ferrocene.

69. The method of Claim 67 wherein said metallocene is a ferrocene derivative.

**EVIDENCE APPENDIX**

None

**RELATED PROCEEDINGS APPENDIX**

None